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Case Report

Anesthetic management of comprehensive dental restoration in a child with glutaric aciduria type 1 using volatile sevoflurane

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Abstract

Glutaric aciduria type 1 (GA1) is a rare, inherited mitochondrial disorder that results from deficiency of mitochondrial glutaryl-CoA dehydrogenase. Most patients develop neurological dysfunction early in life, which leads to severe disabilities. We present a 37-month-old girl with GA1 manifested as macrocephaly and hypotonia who received comprehensive dental restoration surgery under general anesthesia with sevoflurane. She was placed on specialized fluid management during a preoperative fasting period and anesthesia was administered without complications. All the physiological parameters, including glucose and lactate blood levels and arterial blood gas were carefully monitored and maintained within normal range perioperatively. Strategies for anesthetic management should include prevention of pulmonary aspiration, dehydration, hyperthermia and catabolic state, adequate analgesia to minimize surgical stress, and avoidance of prolonged neuromuscular blockade. We administered general anesthesia with sevoflurane uneventfully, which was well tolerated by our patient with GA1. Additionally, communication with a pediatric geneticist and surgeons should be undertaken to formulate a comprehensive anesthetic strategy in these patients. Copyright © 2014 Elsevier Taiwan LLC and the Chinese Medical Association. All rights reserved.

Keywords: dental restoration; fluid therapy; general anesthesia; glutaryl-CoA dehydrogenase; inhalation anesthetics

1. Introduction

Glutaric aciduria type 1 (GA1) is a rare autosomal recessive disorder with an estimated prevalence of 1:100,000 newborns in a Taiwanese study.¹ This disorder involves a deficiency of mitochondrial glutaryl-CoA dehydrogenase (GCDH), which results in an inborn error of lysine, hydroxyllysine, and tryptophan metabolism.² Excessive organic acids

such as glutaric acid, 3-hydroxyglutaric acid, and glutaconic acid accumulate in the brain and lead to neuronal damage, lymphocyte infiltration, elevated concentrations of inflammatory cytokines and nitric oxide, glial proliferation, atrophy of striatal neurons, and neurologic dysfunction.³ Though newborn screening and early treatment can prevent such neurological damage in most patients with GA1, routine treatment does not protect against the encephalopathic crisis that can be precipitated by fever, gastroenteritis (GE), and surgery.⁴ Therefore, intensified emergency treatment targeting prevention or reversal of encephalopathic crisis has been recommended to commence without delay and performed aggressively, especially during surgical intervention.⁵ However, there are only a few reports regarding general anesthesia conducted under either total intravenous anesthesia (TIVA)

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with propofol for ventriculoperitoneal shunting or inhalational anesthesia with sevoflurane for reduction of hip dislocation in patients with GA1.^{6,7} We report here the anesthetic management with sevoflurane for a 37-month-old girl with GA1 undergoing comprehensive dental restoration surgery.

1.1. Patient consent statement

Written informed consent was signed and obtained from the patient's parent. The authors assured the patient's parent that the information will be published without the patient's name attached and every attempt made to maintain anonymity.

2. Case report

A 37-month-old girl with GA1 who weighed 19 kg and who presented with macrocephaly and hypotonia was scheduled for comprehensive dental restoration surgery for treatment of multiple dental caries. Because glutaric aciduria was suspected during neonatal genetic screening, she was referred to our hospital for diagnosis and treatment on postnatal Day 10. The diagnosis was confirmed by the large amount of urinary glutaric acid along with elevated serum glutarylcarnitine. The patient was treated with oral carnitine supplementation and protein restriction with special formula milk (XLYS, LOW TRY Analog). Magnetic resonance imaging of the brain performed under sedation anesthesia with intravenous midazolam and thiopental at 3 months of age showed prominent extra-axial cerebrospinal fluid space, marked widening of Sylvian fissures and middle cranial fossa, and relative loss of bilateral frontotemporal volume. The patient had a history of repeated upper respiratory tract infection (URI) and GE at her 5-, 9-, and 13-month check-ups. No acute neuromotor deterioration was present, and psychomotor development assessed by the age of 7 months showed no psychological delay except mild motor delay. On preanesthetic clinical examination, the patient was asymptomatic except for macrocephaly, with an occipitofrontal circumference of 53 cm (>97th percentile for age), and hypotonia.

2.1. Anesthetic management

During the preoperative fasting period, the patient received intravenous fluid therapy with 10% dextrose in 0.33% saline with potassium chloride (KCl, at a concentration of 6 mEq/500 mL) infused at 60 mL/hour and 20% intralipid infused at 6 mL/hour. After routine monitors and preoxygenation were applied, anesthesia was induced with atropine (0.01 mg/kg), thiamylal (5 mg/kg), fentanyl (2 µg/kg), and cisatracurium (0.2 mg/kg) under parental accompaniment, and manual ventilation was applied using the Sellick maneuver. The patient underwent nasal intubation intubated with a 5-mm cuffed endotracheal tube, and anesthesia was maintained with sevoflurane (1–1.5 minimum alveolar concentration) in 50% oxygen and cisatracurium 0.03 mg/kg every 60 minutes. A 24-gauge arterial catheter was inserted

into the left radial artery. Mechanical ventilation was targeted at maintaining an end-tidal carbon dioxide level of 35–40 mmHg. The patient's body temperature was maintained between 36°C and 37°C with a warming blanket and intravenous fluid therapy was continued until oral intake resumed. All the physiological parameters, blood levels of glucose and lactate, and arterial blood gas were closely monitored and maintained within normal range perioperatively. Ketorolac (0.5 mg/kg) was intravenously administered 30 minutes before the end of the surgical procedure, which was 5 hours in duration. Neuromuscular blockade was reversed with neostigmine and the patient was extubated without difficulty in the operating room. The patient resumed food intake 8 hours later and was discharged uneventfully the next day.

3. Discussion

GA1 is a rare genetic disorder caused by GCDH deficiency, with organic acid accumulation in the brain and neurodegeneration. Secondary carnitine deficiency will occur as the accumulated organic acids are detoxified by carnitine. Patients with GA1 often present with macrocephaly at birth or dystonia shortly afterward. Brain imaging performed shortly after birth usually shows frontoparietal atrophy with widening of Sylvian fissures and arachnoid cysts, and the brain is vulnerable to head trauma that can lead to acute subdural or retinal hemorrhage.^{3,7} Brain atrophy and neuronal loss following injury to the basal ganglia may be accompanied by symptoms such as dystonia, spasticity, rigidity, posture impairment, and complications that impair oral feeding and communication.^{3,7} Patients usually present with an episode of acute infection accompanied by fever and dehydration, and may become hypotonic, lose head control, and have choreoathetosis similar to seizures. Hypotonia slowly improves over weeks but is then replaced with rigidity and dystonia; therefore, patients may develop severe disability and remain wheelchair-bound. These children develop decreased coordination of swallowing movements and are prone to pulmonary aspiration. Some patients may even require nasogastric tube feeding and later require permanent gastrotomy.⁴ Although these patients have difficulty taking or performing tasks, cognition is usually normal. Acute neurological deterioration or encephalopathic crisis, marked by spasm, dystonia, and lethargy, is caused by glutaric acid passage through the blood–brain barrier.^{7,8} Patients with GA1 will develop neurological damage with complications and reduced life expectancy following encephalopathic crisis, and both pneumonia and encephalopathic crisis are the most common causes of death in these patients.^{3,4,8}

With neonatal screening, early routine treatment with carnitine supplement special restriction diet, and neuroprotective emergency treatment, most patients with GA1 may have protection against encephalopathic crisis and possibly lead a normal life.^{7,9–11} Screening identifies elevated glutarylcarnitine in blood spots, and newborns with positive screening results are then confirmed by urinary

organic acid analysis with subsequent enzyme assay and genetic mutation identification. Carnitine supplementation in combination with dietary treatment with protein restriction supplemented with lysine-free special formulas are all crucial for a good neurological outcome.⁹ Emergency treatment to prevent encephalopathic crisis, including preventing catabolism by administering high-energy intake, reducing organic acid production by transient reduction or omission of natural protein intake, avoiding secondary carnitine depletion, and maintaining normal fluid, electrolyte, and pH status, should be started when patients with GA1 are at risk or during surgery.¹¹

It is important for patients with GA1 to prevent acute encephalopathic crises while undergoing surgery.^{8,11} Strategies for anesthetic management should include prevention of pulmonary aspiration, dehydration, hyperthermia, and catabolic state, adequate analgesia to minimize surgical stress, and avoidance of prolonged neuromuscular blockade. Dehydration can be prevented by maintaining normal fluid and electrolyte status via intravenous fluid as soon as fasting started, and prevention of catabolic state can be achieved by high-energy intake. An intravenous regimen consisting of 10% dextrose in 0.33–0.5 normal saline with KCl supplied at a volume 1.5–2 times the daily amount and intralipid 20% supplemented at a rate of 10% of intravenous fluid therapy has been proposed.⁸ In the current case, we had continuously administered intravenous high-caloric fluid therapy until the resumption of oral intake to prevent dehydration, hypoglycemia, and catabolism. We applied the Sellick maneuver during mask ventilation and endotracheal intubation to avoid pulmonary aspiration as suggested by Hernández-Palazón et al,⁶ but we chose a standard intubation procedure instead of rapid sequence intubation to minimize stress response to endotracheal intubation.

Glutaric aciduria is a disorder caused by a deficiency of the mitochondrial enzyme, and Driessen et al¹² reported no major anesthesia-related complications or adverse events in children with mitochondrial disorders undergoing muscle biopsy under general anesthesia with sevoflurane. Footitt et al¹³ also reported that there were no episodes of malignant hyperthermia attributable to general anesthesia with inhalation anesthetics in patients with mitochondrial disorder. Furthermore, carnitine is an essential cofactor in the transport of long-chain fatty acids into the mitochondria and plays a critical role in fatty acid oxidation, and secondary carnitine deficiency is suggested to play an important role in the neuropathogenesis of GA1. Propofol can provide lipid overload and inhibit oxidative phosphorylation, carnitine palmitoyltransferase transport of long-chain fatty acids, and β -oxidation of fatty acid in mitochondria; therefore, it raises concern about the presence of propofol infusion syndrome and severe metabolic acidosis, especially in patients with mitochondrial disorder, carnitine deficiency, and inadequate carbohydrate intake.^{14–16} Therefore, we chose to induce with thiamylal and maintain general anesthesia with sevoflurane rather than with propofol for both induction and maintenance of general anesthesia in the current case, and general anesthesia was safely conducted with

sevoflurane. Another concern regarding the anesthetic management of patients with GA1 is increased sensitivity and prolonged response to neuromuscular blocking agents. Administration of rocuronium with a bolus dose followed by either a continuous infusion or not had been used in patients with GA1 undergoing cerebrospinal fluid shunting and neurogenic hip dislocation procedures, and intraoperative acceleromyography monitoring was applied to avoid residual or sustained neuromuscular blockade.^{6,7} Despite the absence of intraoperative neuromuscular monitoring in the current case, we used cisatracurium to avoid prolonged muscle relaxation and neostigmine to antagonize neuromuscular blockade at the conclusion of surgery. The patient recovered muscle power and woke up a few minutes later. Tracheal extubation was carried out when the patient was awake with sustained eye opening, stable vital signs, adequate spontaneous respiration, and presence of airway protective reflexes (i.e., swallow, gag, and cough) without clinically residual neuromuscular blockade or prolonged recovery time. Furthermore, to manage surgical stress and pain, we administered fentanyl during anesthetic induction and ketorolac 30 minutes before the end of surgery. Our patient recovered without complications with rapid extubation at the end of surgery, and was not agitated and did not complain of pain in the postanesthesia recovery room.

It is crucial to have a thorough understanding of the pathomechanism and clinical manifestation of GA1 while managing these patients. It is also important to have timely communication with a pediatric geneticist and surgeons ahead of elective surgery, to formulate a comprehensive anesthetic strategy in these patients.⁵ Anesthetic management with strategies to prevent the acute encephalopathic crises during and after surgery is mandatory. In conclusion, we administered general anesthesia with sevoflurane uneventfully, which was well tolerated in our patient with GA1.

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